

REMARKS/ARGUMENTS

This Amendment is in response to the Office Action mailed June 12, 2003, having a three month statutory period for response. Applicants respectfully request reconsideration of the above-identified application in view of the following amendments and remarks, and the accompanying Request for Continued Examination.

The Status of the Claims.

Claims 1-9, 12-17, 51-77 are pending upon entry of this amendment, claims 10-11 being cancelled and claims 58-77 being added herein. Claims 1, 4, and 51-56 are amended herein.

Claims 10 and 11 have been cancelled. Cancellation of these claims is without prejudice, without intent to abandon any originally-claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing these cancelled claims.

Claims 1, 4, and 51-56 are amended herein, and claims 58-77 are added. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 1 and 51-56, support for "enriching internalized library members" can be found throughout the specification. For example, see specification at page 17, lines 15-17, page 41, lines 2-5), page 43, lines 7-10, page 46, lines 13-14, as well as Example 5 (see, for example, page 47, lines 9-12, page 53, line 26 through page 54, line 28, page 55, line 29 through page 57, line 12, and Table 7 (page 52).

With respect to new claims 58-77, support for "removing phage trapped in the extracellular matrix" can be found throughout the specification at, for example, page 18, lines 9-13, page 52, lines 2-16, page 53, lines 2-9, and page 54, lines 11-13.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Drawings.

Attached herewith are formal drawings, as requested by the Examiner in the Office Action mailed 6/12/2003. Applicants note that Figures 1 and 4 have been presented on a single page, as have Figures 3 and 7. No amendments to the drawings have been made.

Rejections under 35 U.S.C. §112, Second Paragraph.

Claims 1-17 and 51-57 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter of the invention. Applicants traverse, to the extent that the rejection applies to the claims as amended.

Claim 1 as amended is not indefinite with respect to washing the target cells

Claim 1 is alleged to be vague and indefinite with respect to the steps of washing of the target cells and internalization of phage. Applicants have amended claim 1 to further clarify the invention; this amendment was made without prejudice and should not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. Applicants submit that the rejection is moot in light of the amended claims and respectfully request that the rejection be withdrawn.

Claim 1 as amended is not indefinite with respect to Culturing one or more Target cells

Claim 1 is alleged to be vague and indefinite with respect to culturing the target cells. Applicants have amended the claim to clarify the antecedent basis issue. Applicants submit that the claim as currently amended is not indefinite, and respectfully request that the rejection be withdrawn.

Claim 1 as amended is not indefinite with respect to Binding of phage to an Internalizing Marker

Claim 1 is alleged to be vague and indefinite with respect to the phrase "can be." Applicants have amended claim 1 to further clarify the invention; this amendment was made without prejudice and should not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. Applicants note that the claim as amended no longer contains this phrase, and respectfully request that the rejections be withdrawn.

Claim 1 as amended is not indefinite with respect to antecedent basis of Bound Library Members

Claim 1 is alleged to be vague and indefinite with respect to the phrase "said phage library bound to an internalizing marker." Applicants have amended claim 1 to further clarify the invention; this amendment was made without prejudice and should not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. Applicants note that the claim as amended no longer contains this phrase, and respectfully request that the rejection be withdrawn.

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Claims 53-56 as amended are not indefinite with respect to Antecedent basis of "Removing"

With respect to the rejections of claims 53-56 based upon antecedent basis issues, Applicants have amended the claims to correct the antecedent basis and respectfully request that the rejections be withdrawn.

Rejections under 35 U.S.C. §112, First Paragraph.

Claim 11 has been cancelled

Claim 11 was rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

While Applicants disagree with the allegation that the subject matter is not supported by the specification, in order to facilitate prosecution, Applicants have cancelled claim 11. Cancellation of this claim is without prejudice, without intent to abandon any originally-claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing this cancelled claim.

Applicants submit that the rejection is moot in light of the amended claims and respectfully request that the rejection be withdrawn.

Claim 1 as amended does not present new matter

Claim 1 was rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicants traverse to the extent that the rejection does not apply to the claim as amended.

With respect to the limitation of a "strong wash," Applicants note that support for the strong wash is found throughout the specification and includes the embodiments listed in the Office Action (e.g., low pH washes, glycine washes, stripping buffer washes, and the like). However, the currently pending claim 1 as amended herein no longer includes the term "strong wash." Applicants submit that the rejection is moot in light of the amended claims and respectfully request that the rejection be withdrawn.

With respect to the methods of detecting internalized library members, Applicants respectfully note that "detecting phage" is not a limitation *per se* of claim 1. The claimed invention provides for "identifying internalized library members of said phage display library."

Applicants submit that the specification does enable a variety of methods for detection of internalized library members, any of which may be employed (and the selection of which is not critical to the claimed method). As stated in the specification, starting at page 27, line 21:

The internalized phage display library members can be identified directly or indirectly. Direct identification can be accomplished simply by visualizing the phage within a cell e.g. via immunofluorescent or confocal microscopy. Phage internalization can be identified by their ability to deliver a reporter gene that is expressed within the cell. The reporter gene can be one that produces a detectable signal (e.g. a fluorescent (e.g. lux, green fluorescent protein, etc.) or colorimetric signal (e.g. HRP, B-galactosidase) or can itself be a selectable marker (e.g. an antibiotic resistance gene). The use of both -galactosidase and GFP as reporter genes in such phage is described herein.

Alternatively, the phage display member can bear a marker (e.g. a label) and cells containing the internalized phage can be detected simply by detection of the label (e.g. in a flow cytometer). The direct methods preferably used for identification of the receptors or cells that are bound after selections are performed. It is noted that cell sorting approaches (FACs) will work with identification of either surface bound or internalized phage. However, an additional level of specificity can be achieved if the cells are first sorted for the presence of internalized phage prior to lysis. Direct methods are also used during the analysis phase to demonstrate that the phage selected are indeed internalized.

Alternatively the internalized phage display library members can be identified indirectly. In indirect detection methods the phage-display library member(s) do not need to be detected while they are present within the cell. It is sufficient that they simply have been internalized.

Indirect identification is accomplished for example, by isolating and expanding the phage that were internalized into the cells as described below. Indirect identification is particularly well suited where the identified phage display library members are going to be used in subsequent rounds of selection or to isolate bacteria harboring monoclonal phage genomes for subsequent monoclonal phage characterization (that is for the analysis of selection results).

Furthermore, the allegation that one of skill in the art would not know how to detect or identify members of a phage display library is clearly erroneous. Viral methodologies and polypeptide analysis techniques are standard laboratory procedures that are entirely within the general level of skill in the art.

The Examiner is respectfully reminded that "[t]he test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art" (MPEP 2164.01).

Applicants respectfully submit that the methods of the present invention are not incomplete without a specific recitation of the method used for detection of internalized library members, and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102.

The rejection of claims 1-7, 12-15 and 53 as presented in the Office Action mailed 9/23/03 was maintained in the present Office Action. Claims 1-7, 12-15 and 53 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Barry et al. (Nature Medicine

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2:299-305, 1996). Applicants traverse to the extent that the rejection does not apply to the claim as amended.

The claims are not anticipated by Barry

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Barry et al. is alleged to teach a method for generating cell targeting ligands using peptide-presenting phage libraries. However, the cited art does not teach or disclose every element of the claims as amended. For example, with respect to claim 1, the reference does not teach or disclose enriching internalized library members by at least 30-fold. Furthermore, with respect to new claim 58, the reference does not teach or disclose methods for selecting a polypeptide that include removing phage trapped in the extracellular matrix.

Applicants submit that the claims as amended are not anticipated by the cited reference, and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §103(a).

The rejection of claims 1-17, 51-54 and 57 as presented in the Office Action mailed 9/23/03 was maintained in the present Office Action. Claims 1-17, 51-54 and 57 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Barry et al. in view of either Van Ewijk et al. (PNAS USA 94:3903-3908, 1997) or Stausbol-Gron et al. (FEBS Letters 39:71-75, 1996). Applicants traverse to the extent that the rejection does not apply to the claim as amended.

A *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention (MPEP 2143.03). As noted previously, Barry does not teach or describe enriching internalized library members by at least 30-fold (amended claim 1) or removing phage trapped in the extracellular matrix (new claim 58). Neither Van Ewijk nor Stausbol-Gron rectify this deficiency. Applicants submit that the first requirement for proving a *prima facie* case of obviousness has not been met, and respectfully request that the rejection be withdrawn.

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CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. **If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested.** Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,



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Attachments:

- 1) A Request for Continued Examination;
- 2) A petition to extend the period of response for 2 months;
- 3) A transmittal sheet;
- 4) A fee transmittal sheet;
- 5) Formal Drawings; and
- 6) A receipt indication postcard.